Published by Oxford University Press on behalf of the International Epidemiological Association 2011 *International Journal of Epidemiology* 2011;1–9
doi:10.1093/ije/dyq260

# Genetic contributions to the association between adult height and testicular germ cell tumors

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**Accepted** 9 December 2010

**Background** Previously, we have shown that increasing adult height is associated with increased risk of testicular germ-cell tumor (TGCT). Recently, a number of single nucleotide polymorphisms (SNPs) have been found to be related to height. We examined whether these SNPs were associated with TGCT and whether they explained the relationship between height and TGCT.

**Methods** We genotyped 15 height-related SNPs in the US Servicemen's Testicular Tumor Environmental and Endocrine Determinants (STEED) case–control study. DNA was extracted from buccal cell samples and Taqman assays were used to type the selected SNPs. We used logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (95%CIs).

**Results** There were 561 cases and 676 controls for analysis. Two SNPs were found to be associated with risk of TGCT, rs6060373 (CC vs TT, OR = 1.51, 95% CI: 1.06–2.15) and rs143384 (CC vs TT, OR = 1.53, 95% CI: 1.09–2.15). rs6060373 is an intronic polymorphism of ubiquinol-cytochrome c reductase complex chaperone (UQCC), and rs143384 is a 5′UTR polymorphism of growth differentiation factor 5 (GDF5). No individual SNP attenuated the association between height and TGCT. Adjustment for all SNPs previously associated with adult height reduced the associations between adult height and TGCT by ∼8.5%, although the *P*-value indicated only weak evidence that this difference was important ($P = 0.26$).

**Conclusions** This novel analysis provides tentative evidence that SNPs which are associated with adult height may also share an association with risk of TGCT.

**Keywords** Body height, case–control studies, epidemiology, polymorphism, single nucleotide, testicular neoplasms

# Report Documentation Page

*Form Approved*
*OMB No. 0704-0188*



| 1. REPORT DATE | 2. REPORT TYPE | 3. DATES COVERED |
|---|---|---|
| **DEC 2010** | | **00-00-2010 to 00-00-2010** |

| 4. TITLE AND SUBTITLE | 5a. CONTRACT NUMBER |
|---|---|
| **Genetic contributions to the association between adult height and testicular germ cell tumors** | 5b. GRANT NUMBER |
| | 5c. PROGRAM ELEMENT NUMBER |
| 6. AUTHOR(S) | 5d. PROJECT NUMBER |
| | 5e. TASK NUMBER |
| | 5f. WORK UNIT NUMBER |
| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)<br>**U.S. Army Center for Health Promotion and Preventive Medicine,Silver Spring ,MD,20901** | 8. PERFORMING ORGANIZATION REPORT NUMBER |
| 9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) | 10. SPONSOR/MONITOR'S ACRONYM(S) |
| | 11. SPONSOR/MONITOR'S REPORT NUMBER(S) |

12. DISTRIBUTION/AVAILABILITY STATEMENT
**Approved for public release; distribution unlimited**

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
|---|---|---|---|---|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | |
| **unclassified** | **unclassified** | **unclassified** | **Same as Report (SAR)** | **9** | |

## Introduction

Testicular germ cell tumors (TGCT) have an unusual incidence pattern relative to the majority of other neoplasms. TGCT incidence peaks at ~30 years and rapidly declines thereafter.[1] Research into TGCT aetiology has, thus, focused upon pre-natal, perinatal and adolescent stages of development. The most consistent factors associated with risk of TGCT are previous history of TGCT, family history of TGCT and cryptorchidism,[2,3] whereas meta-analytic synthesis of the available evidence suggests that inguinal hernia, twinning, maternal bleeding, low birth-order and small sibship size may also be risk factors for TGCT.[4,5]

Previously, we, and others, found that increased adult height is also associated with increased risk of TGCT,[6–14] with the majority of such reports indicating a monotonic relationship. The cause of this association remains largely uninvestigated but may be an important aetiological factor given that average male height and incidence of testicular cancer have both been increasing over several generations with strong cohort effects.[15–18]

Adult height is considered to be determined by both environmental and genetic effects. The quality of early childhood nutrition is thought to be integral to adult height attained, with environmental factors in total being responsible for ~20% of the variability observed.[18] In many populations of Western Europe and North America, the heritability of adult height is estimated to be ~80%.[19–22] Recent agnostic approaches in the form of genome-wide association studies have found several genetic loci associated with adult height which, in combination, have been estimated to explain ~3–4% of the population variability of this polygenic trait.[23,24] We examined whether single-nucleotide polymorphisms (SNPs), previously associated with adult height, could explain the association between adult height and risk of TGCT.

## Materials and Methods

### Study design

The US Servicemen's Testicular Tumor Environmental and Endocrine Determinants (STEED) Study methods have been published in detail elsewhere.[6] Briefly, between April 2002 and January 2005 servicemen aged 18–45 years with at least one serum sample stored in the U.S. Department of Defense Serum Repository (DoDSR, Silver Spring, MD, USA) were eligible for enrolment. By use of a person-specific identifier, the specimens in the DoDSR computerized database were linked to the Defense Medical Surveillance System (DMSS)[25] and to other military medical databases in order to determine which military personnel had developed medical conditions.

For the STEED Study, all men with a sample in the DoDSR who subsequently developed TGCT while on active duty were eligible to participate as cases. Men with a sample in the DoDSR who did not subsequently develop TGCT were eligible to participate as controls. Diagnoses of TGCT were limited to classic seminoma or non-seminoma (embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, teratoma, mixed germ cell tumor); spermatocytic seminoma has a different age distribution and is thought to have an aetiology distinct from other TGCTs. The diagnoses were based on the original pathology reports or on review (6.5%) of the pathology slides.

The study was designed as a pair-matched, case–control study. Reference age (within 1 year), race/ethnicity (White, Black, other) and date of blood draw (within 30 days) were the variables used for matching. This analysis was restricted to Whites. In total, 767 cases and 928 controls were recruited, of whom 720 were matched case–control pairs. Buccal cell samples for DNA extraction were provided by 590 cases and 712 controls and 518 and 613 of these, respectively, were of White race. The study was approved by the institutional review boards of the National Cancer Institute, Bethesda, MD, USA and the Walter Reed Army Institute for Research, Silver Spring, MD, USA.

### Genotype analysis

For this project, we selected the top 12 SNPs associated with adult height from the results of two genome-wide association studies[23,26] and three additional SNPs from the LCORL, HHIP and GDF5 loci because they had a stronger association with height in the PLCO study, which contains only males and is, therefore, potentially more relevant for this study. SNPs with a minor allele frequency of <0.15 were excluded. If two or more SNPs were in linkage disequilibrium ($r^2 \geqslant 0.9$), as determined using male genetic data from the PLCO study,[26] a single SNP was selected, with preference given to exonic SNPs over intronic and then higher minor allele frequency.

Genetic analyses were conducted at the US NCIs Advanced Technology Center Core Genotyping Facility. Before analysis, each DNA sample was quantified and validated using a NanoDrop micro-volume spectrophotometer, fluorescent picogreen quantitation assay and Applied Biosystems Identifiler$^{(TM)}$ kit. For identification of SNP genotyping assays, the SNP500Cancer website (http://snp500cancer.nci.nih.gov) can be searched using dbSNP IDs. Taqman assays were run using 5–10 ng of lyophilized sample DNA in 384-well plate formats on the 7900HT (ABI, Foster City, CA, USA). Call rates for each SNP ranged from 98.9% to 99.6%. For quality control purposes, 95 samples were assayed in duplicate. The concordance for each individual SNP was $\geqslant$98.9% with an average concordance across the 15 SNPs of 99.8%.

### Statistical analysis

Primary analyses sought to assess whether the genotyped SNPs were associated with TGCT or attenuated

the association between adult height and TGCT. Secondary analyses included whether there was an interaction between adult height and each SNP in relation to TGCT risk and whether the SNPs were associated with adult height, the latter model of which used both cases and controls.

Odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated to estimate the association of each SNP with risk of TGCT. For the primary analyses, concerning the binary-dependent outcome of cancer, matched and unmatched analyses were conducted using conditional and unconditional logistic regression, respectively. The unmatched analyses were adjusted for the matching factors of reference age and date of blood draw. As risk estimates from conditional and unconditional logistic regression models were similar, only the results from the unconditional models are presented herein as this methodology allowed inclusion of a greater number of individuals. Additive models were utilized to evaluate possible dose–response relationships generating *P*-values for trends and, where appropriate, the likelihood ratio test was used for comparison of logistic regression models. Adult height was analysed as a continuous and/or categorical (quartiles) variable. For the analysis of each SNP with adult height, residuals from a linear regression which included age and case–control status were used to calculate height *z*-scores ($[x-\mu] / \sigma$). A linear regression of each SNP using an additive model was undertaken to provide an estimate of association with height *z*-score. Statistical analyses were conducted with STATA.[27] All tests were two sided.[28]

## Results

The STEED Study collected buccal cell DNA from 590 TGCT cases and 712 controls, of which 518 and 613, respectively, were of White race. Of these, 492 cases and 579 controls were successfully genotyped for at least one of the SNPs under investigation. The distributions of age were similar for cases and controls, as is to be expected from the matched design. The median age of TGCT incidence was 27 years.

Table 1 shows the SNPs assayed and the results of the first primary analysis: the assessment of SNPs in relation to risk of TGCT. All but one SNP, rs143384 ($P=0.04$) was found to be in Hardy–Weinberg equilibrium in the control population using the arbitrary *P*-value of 0.05. We proceeded with analysis of this SNP, but a cautious interpretation is warranted. Associations with TGCT risk were observed between 2 of the 15 SNPs: rs6060373 ($OR_{CT}=1.13$, 95% CI: 0.87–1.47; $OR_{CC}=1.60$, 95% CI: 1.09–2.34; *P* for trend = 0.02) and rs143384 ($OR_{CT}=0.93$, 95% CI: 0.71–1.22; $OR_{CC}=1.59$, 95% CI: 1.10–2.29; *P* for trend = 0.05). These SNPs were in linkage disequilibrium (LD) ($r^2=0.79$) in this study population and when modelled together, it was not discernable which SNP was dominant in the association with TGCT; all ORs were attenuated to a similar degree.

Each typed SNP was tested for association with adult height among all the cases and controls combined using linear regression of height *z*-score on each SNP using an additive model for encoding of the SNP variable (Table 2). Eleven of the 15 SNPs, representing 9 of the 12 loci, showed the same direction of association as that found from GWA studies of height.[23,24,28] The three SNPs with the strongest associations with adult height were $rs4896582_{\text{minor allele(A)}}$ [$\beta=-0.10$ per height *z*-score unit, standard error (SE) = 0.05, $P=0.03$], $rs4842923_{\text{minor allele(T)}}$ ($\beta=-0.07$ per height *z*-score unit, SE = 0.04, $P=0.08$) and $rs143384_{\text{minor allele(C)}}$ ($\beta=0.09$ per height *z*-score unit, SE = 0.04, $P=0.04$).

For the 492 cases and 579 controls successfully genotyped for at least one SNP, the associations between adult height quartiles and TGCT ($OR_{1st\ quartile}$ = referent; $OR_{2nd\ quartile}=1.39$, 95% CI: 0.98–1.97; $OR_{3rd\ quartile}=1.44$, 95% CI: 1.01–2.06; $OR_{4th\ quartile}=1.74$, 95% CI: 1.20–2.52; *P* for trend = 0.003) were very similar to the estimates derived using the full complement of STEED Study cases and controls.[6] Adjustment in the model for any single SNP had very little effect on the risk estimates derived and this was also true when adult height was analysed as a continuous variable (Supplementary Table). Adjustment for the three SNPs which had a $P<0.1$ in their association with adult height in the STEED Study (rs4896582, rs4842923, rs143384) modestly attenuated the relationship between height and TGCT ($OR_{1st\ quartile}$ = referent; $OR_{2nd\ quartile}=1.30$, 95% CI: 0.91–1.84; $OR_{3rd\ quartile}=1.33$, 95% CI: 0.93–1.90; $OR_{4th\ quartile}=1.66$, 95% CI: 1.14–2.42; *P* for trend = 0.010), although the likelihood ratio test did not provide strong evidence that the observed attenuation was greater than what may have been expected by chance ($P=0.14$). In addition, in a model adjusting for all typed SNPs, the associations between height and TGCT were attenuated further ($OR_{1st\ quartile}$ = referent; $OR_{2nd\ quartile}=1.28$, 95% CI: 0.89–1.84; $OR_{3rd\ quartile}=1.30$, 95% CI: 0.90–1.88; $OR_{4th\ quartile}=1.61$, 95% CI: 1.09–2.37; *P* for trend = 0.015), representing an average 8.5% attenuation of association. However, statistically, there was no strong evidence that this difference was greater than what may have been expected given stochastic variation ($P=0.26$). Lastly, secondary analyses testing for potential interaction between adult height and each SNP with regard to TGCT risk were null (data not shown).

## Discussion

This study tested whether SNPs that are associated with adult height are also associated with risk of TGCT. We have shown tentative evidence that two

**Table 1** An analysis of SNPs in relation to testicular germ cell tumour risk in the STEED Study, 2002–05

| dbSNP ID | Chromosome, nt position | Nearby gene(s) | Genotype | Controls | TGCT | | |
|---|---|---|---|---|---|---|---|
| | | | | *n* | *n* | OR[a] (95% CI) | *P*-value |
| rs12735613 | 1, 118 685 496 | *SPAG17* | CC | 338 | 285 | Referent | |
| | HWE $P=0.72$ | | CT | 207 | 177 | 1.02 (0.79–1.31) | 0.91 |
| | | | TT | 28 | 26 | 1.13 (0.64–1.97) | 0.68 |
| | | | *per allele* | *573* | *488* | *1.04 (0.84–1.27)* | *0.74* |
| rs3791675 | 2, 55 964 813 | *EFEMP1* | GG | 317 | 294 | Referent | |
| | HWE $P=0.38$ | | AG | 225 | 170 | 0.82 (0.63–1.06) | 0.12 |
| | | | AA | 32 | 28 | 0.94 (0.55–1.61) | 0.83 |
| | | | *per allele* | *574* | *492* | *0.89 (0.73–1.08)* | *0.24* |
| rs724016 | 3, 142 588 260 | *ZBTB38* | AA | 196 | 152 | Referent | |
| | HWE $P=0.27$ | | AG | 267 | 229 | 1.11 (0.84–1.46) | 0.46 |
| | | | GG | 111 | 108 | 1.27 (0.90–1.78) | 0.17 |
| | | | *per allele* | *574* | *489* | *1.12 (0.95–1.33)* | *0.18* |
| rs16896068 | 4, 17 553 938 | *LCORL* | CC | 414 | 352 | Referent | |
| | HWE $P=0.16$ | | CT | 144 | 127 | 1.03 (0.78–1.36) | 0.86 |
| | | | TT | 19 | 11 | 0.69 (0.32–1.47) | 0.34 |
| | | | *per allele* | *577* | *490* | *0.95 (0.76–1.20)* | *0.69* |
| rs2061455 | 4, 17 644 348 | *LCORL* | TT | 413 | 353 | Referent | |
| | HWE $P=0.16$ | | CT | 146 | 125 | 0.99 (0.75–1.31) | 0.94 |
| | | | CC | 19 | 11 | 0.69 (0.32–1.47) | 0.33 |
| | | | *per allele* | *578* | *489* | *0.93 (0.74–1.18)* | *0.55* |
| rs1492819 | 4, 145 838 863 | *HHIP* | CC | 156 | 149 | Referent | |
| | HWE $P=1.00$ | | CT | 287 | 238 | 0.86 (0.65–1.14) | 0.30 |
| | | | TT | 130 | 102 | 0.83 (0.59–1.16) | 0.27 |
| | | | *per allele* | *573* | *489* | *0.90 (0.76–1.07)* | *0.25* |
| rs1492820 | 4, 145 869 471 | *HHIP* | AA | 161 | 153 | Referent | |
| | HWE $P=0.61$ | | AG | 291 | 244 | 0.88 (0.66–1.16) | 0.35 |
| | | | GG | 120 | 93 | 0.82 (0.58–1.16) | 0.27 |
| | | | *per allele* | *572* | *490* | *0.90* (0.76–1.07) | *0.25* |
| rs4549631 | 6, 127 008 001 | *LOC387103, RSPO3* | TT | 148 | 126 | Referent | |
| | HWE $P=1.00$ | | CT | 287 | 230 | 0.96 (0.71–1.29) | 0.78 |
| | | | CC | 140 | 129 | 1.09 (0.78–1.54) | 0.60 |
| | | | *per allele* | *575* | *485* | *1.05* (0.88–1.24) | *0.61* |

(continued)

**Table 1** Continued

| dbSNP ID | Chromosome, nt position | Nearby gene(s) | Genotype | Controls | TGCT | | |
|---|---|---|---|---|---|---|---|
| | | | | *n* | *n* | OR[a] (95% CI) | *P*-value |
| rs4896582 | 6, 142 745 570 | *GPR126* | GG | 249 | 232 | Referent | |
| | HWE $P=0.71$ | | AG | 255 | 208 | 0.88 (0.68–1.13) | 0.32 |
| | | | AA | 70 | 49 | 0.75 (0.50–1.13) | 0.17 |
| | | | *per allele* | *574* | *489* | *0.87* (0.73–1.04) | *0.13* |
| rs2282978 | 7, 92 102 346 | *CDK6* | AA | 241 | 211 | Referent | |
| | HWE $P=0.18$ | | AG | 251 | 222 | 1.01 (0.78–1.31) | 0.94 |
| | | | GG | 83 | 55 | 0.76 (0.51–1.12) | 0.16 |
| | | | *per allele* | *575* | *488* | *0.91* (0.76–1.08) | *0.29* |
| rs10512248 | 9, 97 299 524 | *PTCH1* | AA | 258 | 224 | Referent | |
| | HWE $P=0.34$ | | AC | 263 | 213 | 0.93 (0.72–1.21) | 0.60 |
| | | | CC | 55 | 52 | 1.09 (0.72–1.66) | 0.68 |
| | | | *per allele* | *576* | *489* | *1.00 (0.83–1.21)* | *0.97* |
| rs1042725 | 12, 646 44 614 | *HMGA2* | CC | 144 | 124 | Referent | |
| | HWE $P=1.00$ | | CT | 288 | 252 | 1.01 (0.75–1.36) | 0.95 |
| | | | TT | 145 | 112 | 0.90 (0.64–1.27) | 0.55 |
| | | | *per allele* | *577* | *488* | *0.95 (0.80–1.13)* | *0.56* |
| rs4842923 | 15, 82 372 908 | *ADAMTSL3* | CC | 141 | 143 | Referent | |
| | HWE $P=0.32$ | | CT | 301 | 232 | 0.76 (0.57–1.02) | 0.07 |
| | | | TT | 135 | 116 | 0.85 (0.60–1.19) | 0.34 |
| | | | *per allele* | *577* | *491* | *0.91 (0.77–1.08)* | *0.30* |
| rs6060373 | 20, 33 377 622 | *GDF5, UQCC* | TT | 233 | 175 | Referent | |
| | HWE $P=0.28$ | | CT | 275 | 232 | 1.13 (0.87–1.47) | 0.36 |
| | | | CC | 66 | 79 | 1.60 (1.09–2.34) | **0.02** |
| | | | *per allele* | *574* | *486* | *1.23 (1.03–1.47)* | ***0.02*** |
| rs143384 | 20, 33 489 170 | *GDF5, UQCC* | TT | 204 | 166 | Referent | |
| | HWE $P=0.04$ | | CT | 299 | 224 | 0.93 (0.71–1.22) | 0.59 |
| | | | CC | 75 | 97 | 1.59 (1.10–2.29) | **0.01** |
| | | | *per allele* | *578* | *487* | *1.19 (1.00–1.42)* | ***0.05*** |

[a]Logistic regression adjusted for reference age and serum date.
Chromosome positions are based on NCBI Build 36.3. HWE, Hardy–Weinberg equilibrium test. Results in italics represent estimates from the per allele, or additive, models whereby genotypes were assessed as ordinal variables entered as continuous exposures in logistic regression models. P values in bold are less than or equal to 0.05.

**Table 2** An analysis of SNPs in relation to adult height in the STEED Study, 2002–05

| dbSNP ID | Chromosome, nt position | Nearby gene(s) | MAF (allele) | | Standard error | *P*-value |
|---|---|---|---|---|---|---|
| rs12735613 | 1, 118 685 496 | *SPAG17* | 0.23 (T) | *−0.05* | 0.05 | 0.34 |
| rs3791675 | 2, 55 964 813 | *EFEMP1* | 0.25 (A) | *−0.04* | 0.05 | 0.46 |
| rs724016 | 3, 142 588 260 | *ZBTB38* | 0.43 (G) | *0.06* | 0.04 | 0.14 |
| rs16896068 | 4, 17 553 938 | *LCORL* | 0.16 (T) | *−0.07* | 0.06 | 0.25 |
| rs2061455 | 4, 17 644 348 | *LCORL* | 0.16 (C) | *−0.08* | 0.06 | 0.20 |
| rs1492819 | 4, 145 838 863 | *HHIP* | 0.48 (T) | 0.04 | 0.04 | 0.34 |
| rs1492820 | 4, 145 869 471 | *HHIP* | 0.46 (G) | 0.05 | 0.04 | 0.25 |
| rs4549631 | 6, 127 008 001 | *LOC387103, RSPO3* | 0.49 (C) | −0.04 | 0.04 | 0.33 |
| rs4896582 | 6, 142745 570 | *GPR126* | 0.34 (A) | *−0.10* | 0.05 | **0.03** |
| rs2282978 | 7, 92 102 346 | *CDK6* | 0.36 (G) | *0.03* | 0.04 | 0.45 |
| rs10512248 | 9, 97 299 524 | *PTCH1* | 0.32 (C) | *0.06* | 0.05 | 0.24 |
| rs1042725 | 12, 64 644 614 | *HMGA2* | 0.50 (T) | 0.02 | 0.04 | 0.72 |
| rs4842923 | 15, 82 372 908 | *ADAMTSL3* | 0.49 (T) | *−0.07* | 0.04 | **0.08** |
| rs6060373 | 20, 33 377 622 | *GDF5, UQCC* | 0.35 (C) | *0.04* | 0.04 | 0.31 |
| rs143384 | 20, 33 489 170 | *GDF5, UQCC* | 0.39 (C) | *0.09* | 0.04 | **0.04** |

Linear regression of age and case-control adjusted height *z*-scores using an additive model. Effect size (β) and standard error are expressed per unit of height *z*-score and *P* values are uncorrected for multiple comparisons. The direction of the effect is given for the minor allele of the control population. Beta estimates in italics are in agreement for the direction of effect compared with what is expected from previous GWAS analyses and LD patterns. Abbreviations: STEED, Servicemen's Testicular Tumor Environmental and Endocrine Determinants; MAF, minor allele frequency. Chromosome positions are based on NCBI Build 36.3. *P* values in bold are less than or equal to 0.1.

of the 15 SNPs analysed, rs6060373 and rs143384, are associated with an increased risk of TGCT. Adjustment for the typed SNPs modestly attenuated the association between adult height and TGCT risk. However, the best fitting models from genome-wide association studies of adult height have only been able to account for 2–4% of its heritability, a small proportion relative to that estimated from twin and family studies (70–90%). Thus, any analysis of the genetic basis of adult height and cancer risk will be somewhat limited; a further analysis of a larger sample size may well provide more robust estimates of association, potentially confirming the findings presented herein.

Both SNPs (rs6060373 and rs143384) found to be associated with TGCT risk are located at chromosome 20q11.22. rs143384 is a 5′ UTR polymorphism of the gene *growth/differentiation factor 5* (*GDF5*), whereas rs6060373 is an intronic variant of *ubiquinol-cytochrome c reductase complex chaperone* (*UQCC*) downstream of GDF5. Many SNPs in this region, including rs6060373 and rs143384, are in linkage disequilibrium and associated with adult height.[23,28,29] Due to the high degree of linkage between rs6060373 and rs143384 in our study, we could not elucidate which SNP was principally associated with TGCT risk. In a subgroup analysis of African–American samples, Sanna *et al*.[29] suggested that SNPs of *GDF5* are more likely to be causal variants of adult height compared with SNPs within *UQCC*, thus the same may be true of TGCT if height is considered to be on the causal pathway between genetic polymorphisms and TGCT risk. SNPs within this region have also been associated with numerous skeletal abnormalities[23,29] including osteoarthritis, for which there is evidence that the causal SNP is rs143383—a 5′ UTR polymorphism which influences *GDF5* transcriptional activity in chondrogenic and non-chondrogenic cell lines.[30,31] In our study, we found the C allele of rs143384 to be associated with an increased risk of TGCT as well as increased height. rs143384-C is in linkage disequilibrium with the C allele of rs143383, which produces higher levels of *GDF5* expression. In addition, *GDF5* is known to be expressed in testicular tissues including germ cells (GDS596).[32] Given that *GDF5* is a member of the TGF-β superfamily of genes which regulate cell growth and differentiation in both embryonic and adult tissues, the sum of evidence presents a plausible hypothesis that *GDF5* polymorphisms may modify TGCT risk.[24,28,32–38]

Genetic polymorphisms that contribute to variation in adult height only slightly attenuated the association between adult height and TGCT risk. Elucidation and addition to our models of polymorphisms that account for a greater proportion of the estimated hereditability of this trait may provide additional resolution to the complexity of these relationships. In addition, environmental exposures are also a key influence in determining adult height; exposures such as early childhood nutrition are plausible

mediators of the relationship between adult height and cancer risk.

Growth within the first 2 years of life is largely predictive of secular trends in adult height,[18] underlining the fact that environmental exposures, which contribute ~20% of variability to adult height in most modern, developed countries, are mainly active within a short time-window during early post-natal development. This is relevant to TGCT not only because this malignancy is considered to have an aetiology rooted in early development, but also because TGCT incidence rates[39] have closely followed secular trends in height.[18,40,41] Both height and TGCT incidence increased in the early part of the 20th century and then underwent a slight decline, from ~1925–40, before subsequently increasing again until the present day. The increases in adult height, estimated to be ~10 mm per decade in Western European countries,[42] are thought to be attributable to various factors associated with socio-economic status, particularly nutritional quality during pre-natal and early childhood development.[18] Although trends of height, energy restriction and TGCT incidence are not entirely congruent across geographies,[39–41] hypotheses of specific nutrient deficiencies remain plausible.

Strengths of this analysis include its population-based design, relatively large sample size and high response rate. In addition, the male US military population is not limited to any geographical area or subset of the population, which makes results from this study generalizable to larger US populations. The STEED Study also included only pathologically confirmed TGCT, ensuring a highly homogenous population from which precise estimates of risk may be attained. This analysis also has certain limitations. Only TGCT cases diagnosed during active duty were identified for enrolment in the case series of the study, which may have somewhat reduced the potential sample size of the study. In addition, the inability to contact men due to deployment presents a potential bias in that deployed men might be different in some way compared with non-deployed men. However, as the majority of young men in military service are healthy and fit it would seem unlikely that this would confer substantial bias, especially given that one would not expect deployed and non-deployed people to differ genetically. The analysis had limited power to assess some of the secondary aims, particularly within strata of height and histology. More important, perhaps, is the reduced power due to the weak effects of the majority of SNPs associated with height, especially given the polygenetic nature of this trait and only having typed 15 SNPs. The small number of non-White participants precluded an examination of differences in risk by ethnicity.

In conclusion, we find indicative associations between two SNPs, in LD, within the *UQCC-GDF5* region on chromosome 20 and risk of TGCT. In addition, adjustment for all typed SNPs reduced the associations between adult height and TGCT by ~8.5% but this reduction was statistically weak ($P = 0.26$). Larger studies should examine a broader scope of height-related SNPs in relation to the relationship between adult height and TGCT risk, in an attempt to assess a larger proportion of the genetic variability of adult height. If our findings are confirmed, further studies designed to further elucidate the mechanism of association would be warranted.

## Supplementary data

Supplementary data are available at *IJE* online.

## Funding

Intramural Program of the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

## Acknowledgements

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense. The authors wish to thank Ms Emily Steplowski of IMS for her contributions to data management.

**Conflict of interest:** None declared.

**KEY MESSAGES**

- The association between adult height and testicular cancer risk has been consistently reported in the literature but the mechanism of association is not understood.
- Recent genome-wide association studies have found SNPs associated with adult height which we apply here to a model of adult height and testicular cancer.
- We present tentative evidence that SNPs which are associated with adult height may also share an association with risk of testicular cancer.

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